Knoll Pharmaceutical Company

October 25, 1999

1658 '99 OCT 26 A9:27

BASF Pharma

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 99D-2635

To Whom It May Concern:

This letter contains Knoll Pharmaceutical Company's comments on the Draft Guidance found in the Federal Register dated August 27, 1999 entitled "ANDA's: Blend Uniformity Analysis". It is Knoll's position that enactment of this industry guidance will increase the cost of drug products without a commensurate increase in assurance of product quality.

Pharmaceutical manufacturers comply with the requirements of 211.110(a)(3) by conducting appropriate mixture and dosage unit uniformity testing during validation studies, then monitoring routine production to verify that the validated manufacturing parameters are maintained.

Validation studies typically include measurements of mixture uniformity as well as uniformity of dosage forms (they also involve establishing ranges for in-process tests such as weight, hardness, disintegration and friability in the case of solid/oral dosage forms). Both types of data are critical because they provide uniformity information at different stages of the process that should be in agreement. Lack of agreement suggests that the process needs further evaluation. However, experience has demonstrated that mixture uniformity data are subject to greater variability caused by sampling techniques and equipment and, as such, may be less reliable then uniformity tests on the individual dosage units. Mixture uniformity testing becomes even more variable and subject to error with low dose, low weight formulations and as the number of active pharmaceutical ingredients in the formulation increases.

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3000 Continental Drive-North, Mount Olive, New Jersey 07828-1234 (973) 426-2600

Mixture uniformity is not an appropriate in-process test because a process adjustment, based upon test results, is not possible. This is because mixing parameters were established during validation studies and parameter ranges cannot be exceeded without approval of the Quality Control Unit. The true in-process tests for solid/oral dosage forms, for example, are weight, hardness, disintegration and friability; manufacturing personnel when ranges for these parameters, established during validation studies, are exceeded can make adjustments in machine operating parameters.

Another undesirable situation that would result from implementing this industry guidance would be increased manufacturing cycle times. Manufacturing personnel would have to wait for mixture uniformity test results from Quality Control before the mixer could be unloaded. This would result in additional equipment and personnel time with a corresponding increase in manufacturing costs.

In summary, the requirements of 211.110(a)(3) regarding mixture uniformity are best met by performing appropriate validation studies that establish operating ranges for key process control parameters, then monitoring routine batch manufacturing to assure the process is maintained with-in these validated parameter ranges. Mixture uniformity testing will increase product costs without improving the assurance of product quality.

Thank you very much for the opportunity to comment on this draft guidance document.

Sincerely,

Doug Kollmorgen/GTB

Douglas Kollmorgen

Senior Director, Quality Assurance

Knoll Pharmaceutical Company

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